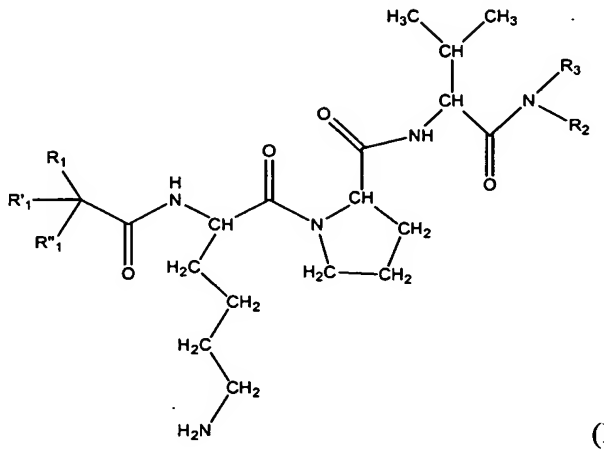
CLAIMS

1. A solution synthesis method for a KPV tripeptide diamide derivate represented by the following formula (I)



(I),

or for a salt thereof, independently from the stereochemistry of the implemented amino acids wherein:

a) R_1, R'_1 and R''_1 represent, independently from each other, a hydrogen atom or

- a linear or branched C_1-C_{22} alkyl moiety, optionally interrupted by a heteroatom such as O or N or S or Si,

- C_4-C_{10} cycloalkyl moiety,

- a linear or branched C_1-C_{22} polyfluoroalkyl or perfluoroalkyl moiety,

- an aryl moiety optionally substituted by one or more halogen atoms such as Cl, F, Br or I or one or more linear or branched C_1-C_4 alkyl moieties,

- an aralkyl moiety,

- or R_1 and R'_1 could form with $C(R''_1)$ a saturated ring with from 3 to 7 atoms, optionally substituted by one or more linear or branched C_1-C_4 alkyl moieties and/or optionally containing a heteroatom such as O, S or N,

with the proviso that the $R_1(R'_1)(R''_1)CO$ group does not represent an amino acid residue or a peptide residue;

b) R_2 and R_3 represent, independently from each other, a hydrogen atom or represent

- a linear or branched C_1-C_{24} alkyl moiety, optionally interrupted by a heteroatom such as O or N or S or Si,

- a C_4-C_{10} cycloalkyl moiety,

- a linear or branched C_1-C_{22} polyfluoroalkyl or perfluoroalkyl moiety,

- an aryl moiety optionally substituted by one or more halogen atoms such as Cl, F, Br or I, or one or more linear or branched C_1-C_4 alkyl moieties,

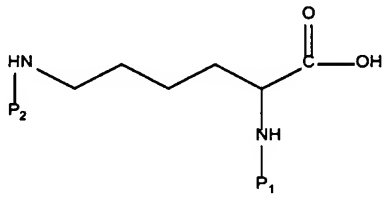
- an aralkyl moiety,

- or R_2 and R_3 could form with the nitrogen atom a saturated ring with from 5 or 6 atoms optionally substituted by one or more linear or branched C_1-C_4 alkyl moieties, said saturated ring optionally containing a heteroatom such as O, S or also an additional nitrogen atom,

with the proviso that the $N(R_2)$ (R_3) group does not represent an amino acid or a peptide residue;

said method comprising:

a) reacting a lysine diprotected residue having the following formula (II):

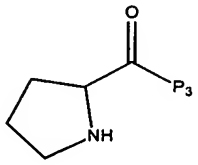


(II),

optionally salified by a mineral or organic base,

wherein P_1 and P_2, may be the same or diffient and each represent independently from one another a protective group,

with a Proline residue having the following formula (III):

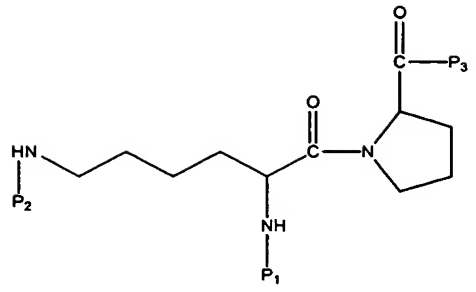


(III)

optionally salified by a mineral or organic acid,

wherein P_3 represents a protective group differing from any of the P_1 and P_2 protective groups, or wherein P_3 represents a hydroxyl group,

in the presence of an activation reagent or a coupling reagent in a solvent, so as to obtain the following compound having the formula (IV):

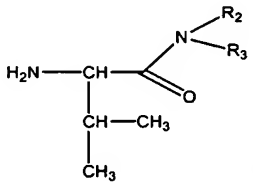


(IV)

wherein P_1, P_2 and P_3 have the above-mentioned meanings,

b) and, in any order,

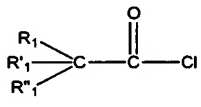
1) coupling a valine compound having the following formula (V) on the C-terminal function of the Proline residue of the compound with formula (IV) wherein P_3 represents OH,:



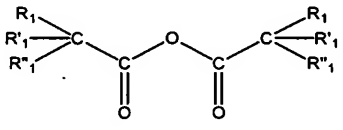
(V),

wherein R_2 and R_3 have the same meanings as hereinabove, and removing the P_1 protective group,

2) amidating the $NH_2(\alpha)$ group in a N-terminal position of the lysine residue by a compound having the following formula (VI-A) or (VI-B):

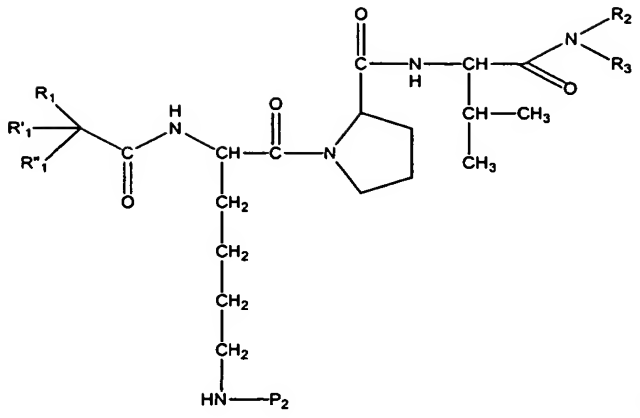


(VI-A)



(VI-B),

so as to obtain the following compound having the formula (XII):



(XII),

wherein P_2, R_1, R'_1, R''_1, R_2 and R_3 have the same meaning as hereinabove;

c) removing the P_2 protective group from the compound having the formula (XII) so as to obtain the compound having the formula (I), optionally under the form of a mineral or organic salt.

2. The method according to claim 1, wherein the compound having the formula (I) is a salt selected amongst the hydrochlorides, hydrobromides, sulphates, acetates, citrates, tartrates, lactates, phosphates, hydrogenophosphates, propionates and succinates.

3. The method according to claims 1 or 2, wherein the Lysine, Proline or Valine amino acid residues are any of the stereoisomers of such residues.

4. The method according to claims 1 or 2, wherein the salt is obtained during step c) through introducing the corresponding acid.

5. The method according to claim 4, wherein the acid is acetic acid, hydrochloric acid, hydrobromic acid, sulphuric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, hydrogenophosphoric acid, propionic acid or succinic acid.

6. The method according to claim 5, wherein the acid is acetic or hydrochloric acid.

7. The method according to claims 1 or 2, wherein the P_1 andP_2 protective groups represent, independently from each other, Adoc (=1-adamantyloxycarbonyl) BOC (=t-butyloxycarbonyl), 2-bromo-Z (=2-bromo-benzyloxycarbonyl), 2-chloro-Z (=2-chloro-benzyloxycarbonyl), Fmoc (= 9-fluorenylmethoxycarbonyl), Formyl, Nicotinoyl, 4-nitro-Z (=4-nitro-benzyloxycarbonyl), Tfa (=trifluoroacetyl), Tos (=p-toluenesulfonyl), Z(=benzyloxycarbonyl)or Adpoc (=1-(adamantyl)-1-methylethoxycarbonyl).

8. The method according to claims 1 or 2, wherein the P_1 and P_2 protective groups are selected such as to be removed respectively in distinct operating conditions.

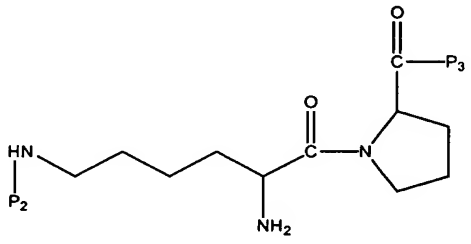
9. The method according to claims 1 or 2, wherein the compound having the formula (II) is salified by an organic base, preferably an organic amine.

10. The method according to claims 1 or 2, wherein the compound having the formula (III) is salified by a mineral or an organic acid.

11. A method according to claims 1 or 2, wherein in step a), the peptide coupling reaction occurs in the presence of an activation or a coupling reagent selected amongst carbodiimides , water-soluble carbodiimides, phosphonium salts, PyBOP (=(benzotriazol-1-yloxy)tripyrrolidino-phosphonium hexafluorophosphate), PyBROP (=bromotripyrrolidino-phosphonium hexafluorophosphate), PyCloP (=chlorotripyrrolidino-phosphonium hexafluorophosphate), or also by means of reagents selected amuongst PyClU (=chloro-N,N,N',N'-bis(tetramethylene)formamidinium hexafluoro-phosphate), N-hydroxysuccinimide, EEDQ (=1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinolin), CDI (=carbonyldiimidazole), or chloroformates

12. The method according to claims 1 or 2, wherein the step b) further comprises the following steps :

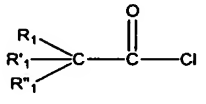
b1) removing the P_1 protective group of the compound with formula (IV) wherein P_3 represents a protective group, so as to obtain the compound with formula (IX):



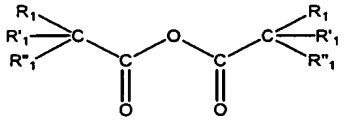
(IX)

wherein P_1 has the same meaning as in claim 1 and P_3 represents a protective group;

b2) amidating the $NH_2(\alpha)$ group of the lysine residue of the compound having the formula (IX) with the following compound having the formula (VI-A) or the compound having the formula (VI-B):

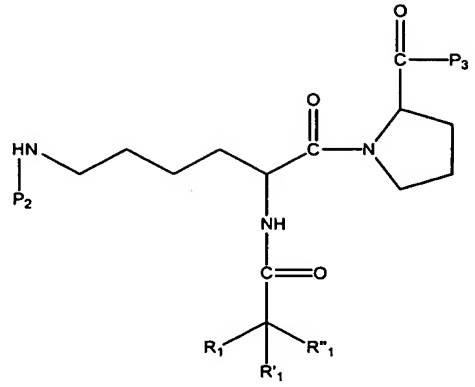


(VI-A)



(VI-B),

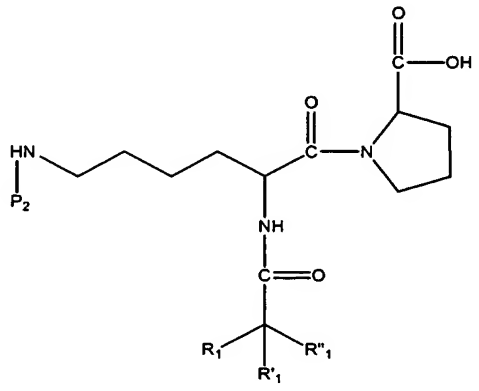
wherein R_1, R'_1 and R''_1 have the same meanings as in claim 1, so as to obtain the following compound with formula (X);



(X)

wherein R_1, R'_1, R''_1, P_1 have the same meaning as in claim 1 and P_3 represents a protective group;

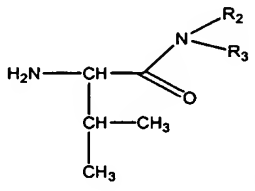
b3) Removing the P_3 protective group from the compound having formula (X) so as to obtain the compound with formula (XI):



(XI)

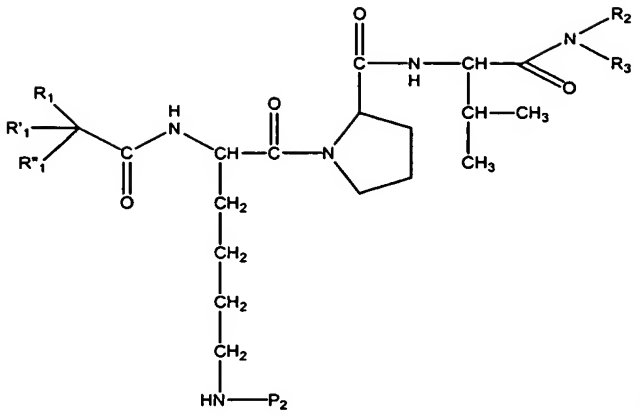
wherein R_1, R'_1, R''_1 and P_2 have the same meaning as in claim 1;

b4) coupling the compound having formula (XI) with the valine compound having the following formula (V), optionally salified by a mineral or organic acid:



(V),

wherein R_2 and R_3 have the same meaning as hereinabove, so as to obtain the following compound having formula (XII):

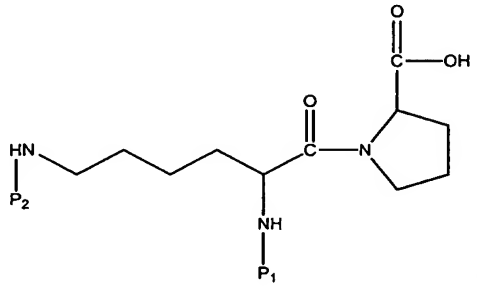


(XII),

wherein P_2, R_1, R'_1, R''_1, R_2 and R_3 have the same meanings as hereinabove.

13. The method according to claims 1 or 2, wherein the step b) further comprises the following steps :

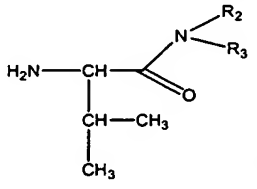
b5) removing group P_3 from the compound having formula (IV) where the P_3 group represents a protective group, so as to obtain the compound with the following formula (VII):



(VII),

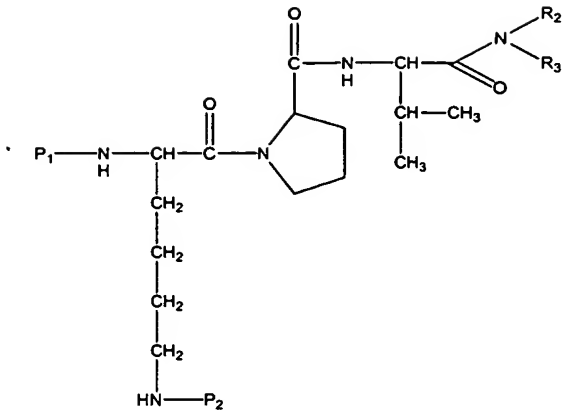
wherein P_1 and P_2 have the same meanings as in claim 2;

b6) coupling the compound having formula (VII) with the valine compound having the formula (V), optionally salified by a mineral or an organic acid:



(V),

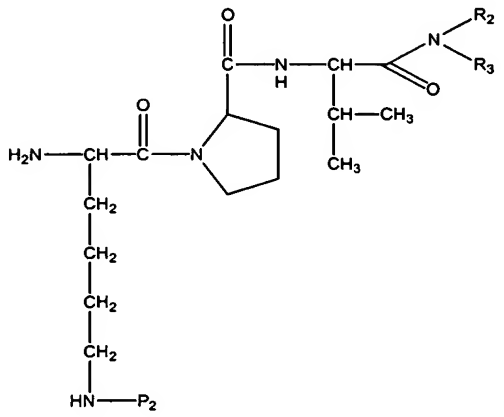
wherein R_2 and R_3 have the same meaning as in claim 1 so as to obtain a compound having formula (XIII):



(XIII)

wherein P_1, P_2, R_2 and R_3 have the same meaning as hereinabove ;

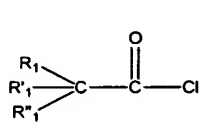
b7) removing the P_1 protective group from the compound having the formula (XIII) so as to obtain the following compound having the formula (XIV), and optionally salified by a mineral or an organic acid:



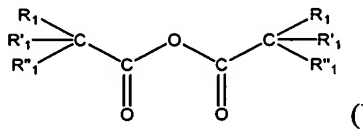
(XIV)

wherein P_2, R_2 and R_3 have the same meaning as hereinabove ;

b8) amidating the $NH_2(\alpha)$ group of the lysine residue of the compound having the formula (XIV) with the compound having the formula (VI-A) or the following compound having the formula (VI-B), optionally mineralized by a mineral or an organic acid:

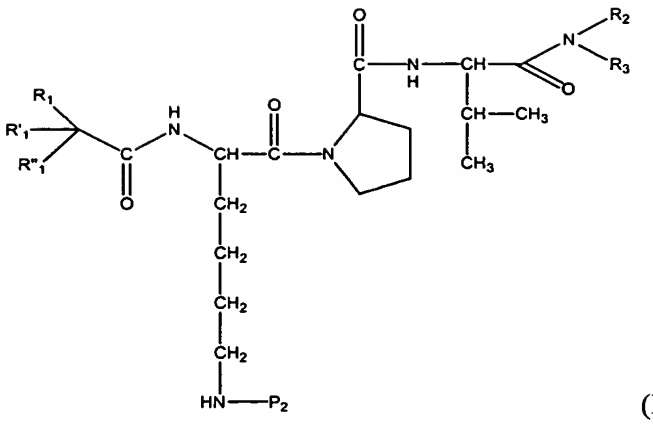


(VI-A)



(VI-B)

wherein R_1, R'_1 et R''_1 have the same meanings as in claim 1, so as to obtain the following compound having the formula (XII):

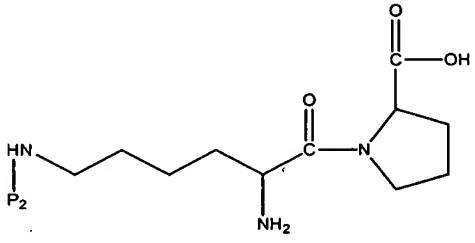


(XII),

wherein P_2, R_1, R'_1, R''_1, R_2 and R_3 have the same meanings as hereinabove.

14. The method according to claims 1 or 2, whereinstep b) further comprises the following steps :

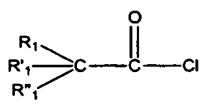
b9) removing the P_1 protective group from the compound having the formula (VII) wherein the P_3 group represents a hydroxy group so as to obtain the following compound having the formula (XV):



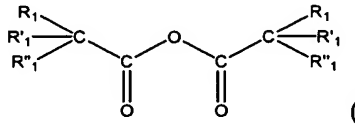
(XV)

wherein P_2 has the same meaning as in claim 2;

b10) amidating the $NH_2(\alpha)$ group of the lysine residue of the compound having the formula (XV) with the compound having the formula (VI-A) or the following compound having the formula (VI-B):



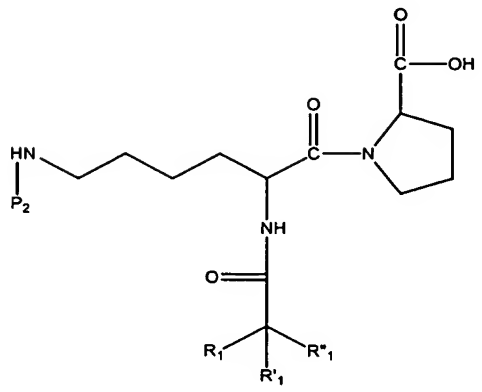
(VI-A)



(VI-B)

wherein R_1, R'_1 et R''_1 have the same meanings as in claim 1,

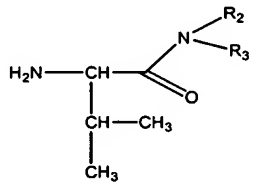
so as to obtain the following compound (XI), optionally salified by an organic or a mineral base:



(XI)

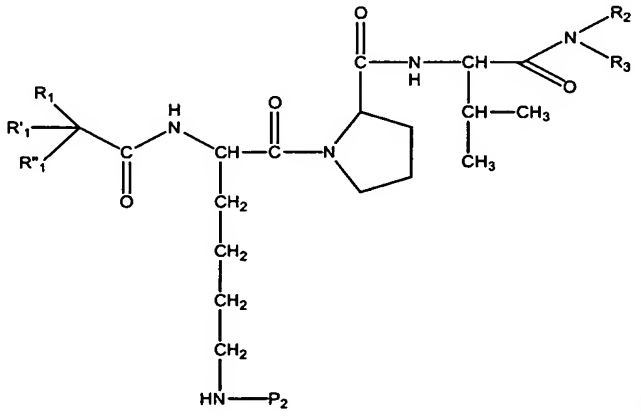
wherein P_2, R_1, R'_1 et R''_1 have the same meaning as hereinabove ;

b11) coupling the compound having the formula (XI) with the valine following compound having the formula (V), optionally salified by a mineral or an organic acid:



(V)

wherein R_2 et R_3 have the same meanings as in claim 1; so as toobtain the compound of the formula (XII):



(XII),

wherein P_2, R_1, R'_1, R''_1, R_2 and R_3 have the same meaning as hereinabove.

15. The method according to claims 1 or 2, wherein in the compound having the formula (II), the P_1 protective group is t-butyloxycarbonyl (BOC) and the P_2 protective group is benzyloxycarbonyl (Z).

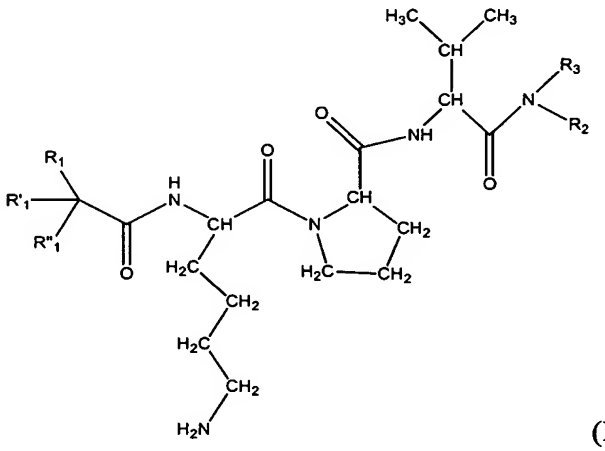
16. The method according to claims 1 or 2, wherein in the compound of the formula (III), the P_3 protective group is the OBzl benzyl ester group.

17. The method according to claims 1 or 2, wherein in the compound having the formula (I), the R_1, R'_1 and R''_1 group represent each a hydrogen atom.

18. The method according to claims 1 or 2, wherein in the compound having the formula (I), the R_2 and R_3 groups represent each a hydrogen atom.

19. The method according to claims 1 or 2, wherein the P_1 protective group is t-butyloxycarbonyl (BOC), the P_2 protective group is benzyloxycarbonyl (Z) and the P_3 protective group is OBzl benzyl ester.

20. A KPV tripeptide diamide derivate or salt thereof represented by the following formula (IA):



(IA)

wherein:

a) R_1, R'_1 and R''_1 represent, independently from each other, a hydrogen atom or

- a linear or branched C_1-C_{22} alkyl moiety, optionally interrupted by a heteroatom such as O or N or S or Si,

- C_4-C_{10} cycloalkyl moiety,

- a linear or branched C_1-C_{22} polyfluoroalkyl or perfluoroalkyl moiety,

- an aryl moiety optionally substituted by one or more halogen atoms such as Cl, F, Br or I or one or more linear or branched C_1-C_4 alkyl moieties,

- an aralkyl moiety,

- or R_1 and R'_1 could form with $C(R''_1)$ a saturated ring with from 3 to 7 atoms, optionally substituted by one or more linear or branched C_1-C_4 alkyl moieties and/or optionally containing a heteroatom such as O, S or N,

- hydrogen,

with the proviso that the $R_1(R'_1)(R''_1)CO$ group does not represent an amino acid residue or a peptide residue with at least one of R_1, R'_1, R''_1 being different from hydrogen.

b) R_2 and R_3 represent, independently from each other, a hydrogen atom or represent

- a linear or branched C_1-C_{24} alkyl moiety, optionally interrupted by a heteroatom such as O or N or S or Si,

- a C_4-C_{10} cycloalkyl moiety,

- a linear or branched C_1-C_{22} polyfluoroalkyl or perfluoroalkyl moiety,

- an aryl moiety optionally substituted by one or more halogen atoms such as Cl, F, Br or I, or one or more linear or branched C_1-C_4 alkyl moieties,

- an aralkyl moiety,

- or R_2 and R_3 could form with the nitrogen atom a saturated ring with from 5 or 6 atoms optionally substituted by one or more linear or branched C_1-C_4 alkyl moieties, said saturated ring optionally containing a heteroatom such as O, S or also an additional nitrogen atom, with at least one of the residues R2 or R3 being different from hydrogen,

with the proviso that the $N(R_2)$ (R_3) group does not represent an amino acid or a peptide residue.

21. The KPV tripeptide diamide derivative according to claim 20, wherein the salt is selected amongst hydrochlorides, hydrobromides, sulphates, acetates, citrates, tartrates, lactates, phosphates, hydrogenophosphates, propionates and succinates.

22. The KPV tripeptide diamide derivate according to claims 20 or 21, wherein the Lysine, Proline or Valine amino acid residues are any of the stereoisomers of each of such residues.

23. A composition comprising: a KPV tripeptide diamide derivative or salt thereof according to claims 20 or 21 in a physiologically acceptable medium.

24. The composition according to claim 23, wherein the physiologically acceptable medium is a cosmetic medium and the KPV tirpeptide diamide derivate or salt thereof is present in an amount ranging from 10^{-8} to 10^{-3} g/100g.

25. The composition according to claim 23, wherein the physiologically acceptable medium is a pharmaceutical medium and the KPV tirpeptide diamide derivate is present in an amount greater than 5.10^{-4} g/100g.

26. The use of a derivate (IA) according to any of claims 20 to 22 in a cosmetic composition or for producing a dermatologic composition for or designed for treating dry skins and/or sensitive skins.

27. The method according to claim 9, wherein the organic base is an organic amine.

28. The method according to claim 1, further comprising the step of deprotecting P3 prior to coupling said valine compound of Formula (V) to said compound of Formula (IV).

29. A method of treating dry or sensitive skin comprising: obtaining a quantity of a composition of claim 23 and applying said composition to the dry or sensitive skin of a patient.

30. A method of treating dry or sensitive skin comprising: obtaining a quantity of a composition of claim 24 and applying said composition to the dry or sensitive skin of a patient.

31. A method of treating dry or sensitive skin comprising: obtaining a quantity of a composition of claim 25 and applying said composition to the dry or sensitive skin of a patient.